Amendments to the Drawings:

The first attached replacement drawing sheet (Figs. 1 and 2) has been amended to conform to 37 C.F.R. 1.84(l) standards for the character of lines, numbers and letters.

The second attached replacement drawing sheet (Figs. 3 and 4) has been amended to conform to 37 C.F.R. 1.84(l) standards for the character of lines, numbers and letters. Figure 4 has been further amended to replace "retrospelenial" with "retrosplenial."

The third attached replacement drawing sheet (Figs. 5 and 6) has been amended to conform to 37 C.F.R. 1.84(l) standards for the character of lines, numbers and letters.

The fourth attached replacement drawing sheet (Figs. 7 and 8) has been amended to conform to 37 C.F.R. 1.84(l) standards for the character of lines, numbers and letters.

The fifth attached replacement drawing sheet (Fig. 9) has been amended to replace "retroslpenial" with "retrosplenial."

The sixth attached replacement drawing sheet (Fig. 10) has been amended identify the upper and lower panels of Figure 10 as Figure 10A and 10B, respectively. Figure 10 has also been amended to replace " retroslpenial" with "retrosplenial."

The seventh attached replacement drawing sheet (Figs 11 and 12) includes Fig. 11 which has been amended to include a legend.

The eighth attached replacement drawing sheet (Figs. 13 and 14) has been amended to conform to 37 C.F.R. 1.84(l) standards for the character of lines, numbers and letters.

The ninth attached replacement drawing sheet (Fig. 15A) has been amended to correct an obvious error, *i.e.*, "p Malue" has been replaced with "p Value." Support this amendment is provided by the informal Figure 15 as originally filed in U.S. Application No. 09/201,430, filed November 30, 1998, to which the instant application claims priority.

The tenth attached replacement drawing sheet (Fig. 15B) has been amended to correct an obvious error, *i.e.*, "p Malue" has been replaced with "p Value." Support this amendment is provided by the informal Figure 15 as originally filed in U.S. Application No. 09/201,430, filed November 30, 1998, to which the instant application claims priority.

The eleventh attached replacement drawing sheet (Fig. 15C) has been amended to correct an obvious error, *i.e.*, "p Malue" has been replaced with "p Value." Support this amendment is provided by the informal Figure 15 as originally filed in U.S. Application No. 09/201,430, filed November 30, 1998, to which the instant application claims priority.

The twelfth attached replacement drawing sheet (Fig. 15D) has been amended to correct an obvious error, *i.e.*, "p Malue" has been replaced with "p Value." Figure 15D has been further amended to replace "2μg/ml alum" with "2 mg/ml alum." Support for these amendments is provided by the informal Figure 15 as originally filed in U.S. Application No. 09/201,430, filed November 30, 1998, to which the instant application claims priority.

The thirteenth attached replacement drawing sheet (Fig. 15E) has been amended to correct an obvious error, *i.e.*, "p Malue" has been replaced with "p Value." Support this amendment is provided by the informal Figure 15 as originally filed in U.S. Application No. 09/201,430, filed November 30, 1998, to which the instant application claims priority.

The fourteenth attached replacement drawing sheet (Fig. 16) has been amended to orient the words in a left-to-right fashion when the page is turned so that the top becomes the left side. Figure 16 has been further amended to replace "Anti AB" with "Anti-Abeta." Support for this amendment can be found on page 92, lines 25-33 of the specification.

The fifteenth replacement drawing sheet (Fig. 17) has been amended to orient the words in a left-to-right fashion when the page is turned so that the top becomes the left side.

The sixteenth attached replacement drawing sheet (Fig. 18) has been amended to orient the words in a left-to-right fashion when the page is turned so that the top becomes the left side.

16 Replacement Drawing Sheets are submitted herewith.

REMARKS/ARGUMENTS

Claims 1-10 are pending. Claims 11-57 were withdrawn from consideration and are cancelled herein. Support for the amendment to claim 1 is provided at, *e.g.*, sentence bridging pp. 55-56. Applicant responds using the paragraph numbering of the office action.

The Specification

The cross reference to related application section has been replaced with a replacement section which provides domestic priority information for the instant case. An Initial Application Data Sheet (ADS) is submitted herewith to satisfy the specific reference requirement of 35 U.S.C. § 119(e) and § 120.

The paragraphs beginning on page 10, line 12, and page 92, line 5, have been amended to conform with amended Figure 10, *i.e.*, "Figure 10 (upper panel)" has been deleted and replaced with "Figure 10A." "Figure 10 (lower panel)" has been deleted and replaced with "Figure 10B." The paragraph beginning on page 92, line 25 has been amended to correct an obvious error, *i.e.*, "Table 10" has been deleted and replaced with "Table 11."

The paragraphs beginning on page 91, line 17, and page 92, line 3, have been amended to conform the alum concentration to the alum concentration recited in Figure 15 as filed in U.S. Application No. 09/201,430, filed November 30, 1998. The instant application claims priority to U.S. Application No. 09/201,430.

¶2. As requested by the Examiner the phrase "[REMAINDER OF PAGE INTENTIONALLY BLANK]" has been deleted.

¶3. As requested by the Examiner, Figures 11 and 16 have been amended (*see* the Amendments to the Drawings section, above). Replacement drawing sheets are submitted herewith. Also, as requested by the Examiner, the specification has been amended to contain a description of each of figures A-E.

¶4. The Examiner objects to the claims as reciting nonelected material. However, examination following an election of species is not confined to the election of species. "An examiner's action subsequent to an election of species should include a complete action on the merits of all claims readable on the elected species." MPEP § 809.02(c). Accordingly, it is respectfully submitted that cancellation of nonelected material is not required. If the Examiner believes otherwise, he is requested to identify what section of the MPEP his position is based on.

¶¶6-8. Statutory-Type Double Patenting

U.S. Application No. 09/585,817

Claims 1-10 of the instant application are provisionally rejected under 35 U.S.C. § 101 as claiming the same invention as that of claims 1-10 of copending Application No. 09/585,817.

U.S. Application No. 09/724,953

Claims 1-10 of the instant application are provisionally rejected under 35 U.S.C. § 101 as claiming the same invention as that of claims 1-10 of copending Application No. 09/724,953. Claims 1-10 of Application No. 09/724,953 have been canceled, thus, mooting the rejection.

U.S. Application No. 09/724,567

Claims 1-10 of the instant application are provisionally rejected under 35 U.S.C. § 101 as claiming the same invention as that of claims 1-10 of copending Application No. 09/724,567. Claims 1-10 of Application No. 09/724,567 have been canceled, thus, mooting the rejection.

U.S. Application No. 09724,575

Claims 1-10 of the instant application are provisionally rejected under 35 U.S.C. § 101 as claiming the same invention as that of claims 1-10 of copending Application No. 09/724,575. Claims 1-10 of Application No. 09/724,575 have been canceled, thus, mooting the rejection.

U.S. Application No. 09/979,952

Claims 1-10 of the instant application are provisionally rejected under 35 U.S.C. § 101 as claiming the same invention as that of claims 1-57 of copending Application No. 09/979,952. Claims 1-10 of Application No. 09/979,952 have been canceled; and claims 11-28, 40-41, 44-48, and 50-57 have been withdrawn. Applicant proposes that: (1) the provisional rejection of claims 1-10 be withdrawn; and, (2) that the provisional rejection of claims 11-57 be held in abeyance until indication of allowability in the present case.

Claims 1-10 of Application No. 09/979,952 have been canceled. Consequently, they are no longer in conflict under 37 C.F.R. § 1.78 with claims 1-10 of the instant application.

¶¶9-12. Obviousness-Type Double Patenting

Claims 1-10 stand provisionally rejected for obviousness type double patenting over claims in several copending cases. Applicants propose the issues be held in abeyance until indication of allowability in the present case. Applicant will then consider providing a terminal disclaimer over cited cases provided the cited case has been or is about to patented, the claims in the cited case have not been divided from those in the present case by restriction requirement or election of species, and the claims in the cited case are in conflict with those in the present case at this time.

¶¶13-24. Claims 1-10 stand rejected under 35 USC 112, first paragraph for alleged lack of enablement. Due to the length of this rejection, the Examiner's paragraphs will be addressed in turn.

¶14. The Examiner summarizes the claims. No response is needed.

¶15. The Examiner notes that the specification provides examples in which Aβ plus adjuvant is administered to a mouse model of Alzheimer's disease. However, the Examiner alleges that these experiments are not predictive of administration of PrP to treat patients with

prion based disorders. The Examiner further alleges there are no art-accepted PrP animal models. In response, several animals of prion disease were available in the mid-1990s (*see* Baldauf *et al.*, *J. Gen. Virol.* 78, 1187-97 [1997]; and, Telling *et al.*, *Genes Dev.* 10, 1736-50 [1996], copies of which are attached hereto). Moreover, two publications dated after the priority date of the present invention shows that active immunization with PrP and passive administration of antibodies to PrP in a mouse model of prion disorder diseases produces results similar to those described for immunization of Aβ (*see* Sigurdsson *et al.*, *Am. J. Pathol.* 161, 13-17 [2002][1] [active immunization]; Sigurdsson *et al.*, *Neuroscience Letters* 336, 185-187 [2003][2] [passive immunization]). The authors acknowledge that their report represents an extension of previous work relating to Aβ immunization (*see Am. J. Pathol.* at p. 15, second column, first paragraph). The similarity of results for immunization with PrP and Aβ42 in mouse models of prion and Alzheimer's disease respectively indicates that administration of Aβ to Alzheimer's disease is predictive of how administration of PrP or AScr affects patients with prion-related disease.

¶16. The Examiner alleges one would doubt the claimed method would work due to specific biological actions/activities that a prion protein and an adjuvant would effect, lack of information how the immunogenic effect on amyloid deposition relates to symptoms of disease. The Examiner also cites Akiyama *et al.* (2000). These points are addressed in turn. The result that passive administration of prion protein achieves essentially the same results as active administration of prion protein shows that active administration of prion protein acts, at least in part, through formation of antibodies. With respect to how the immunogenic effect of prion administration relates to symptoms of disease, one would expect similar symptomatic effects results from prion administration and Aβ in view of the similarity in pathology and analogous results in mouse models described above.

The relevance of Akiyama is unclear. The reference discusses a potential role for inflammation in Alzheimer's disease. Perhaps the Examiner is alleging that the claimed compositions will not reverse an inflammatory component of Alzheimer's disease or may

[1] Cited by the Examiner in the Office Action mailed July 25, 2003.
[2] Cited as citation no. 396 by the Information Disclosure Statement submitted herewith.

exacerbate it. However, it is submitted that a standard of enablement that requires the claimed compositions to reverse every aspect of Alzheimer's disease and have no side effects is unduly high. Courts have routinely found that the mere identification of a pharmacological activity that is relevant to an asserted pharmacological use is itself "obviously beneficial to the public." *Nelson v. Bowler,* 206 USPQ 881, 883 (CCPA 1980). It follows that that a composition is enabled if the specification in combination with knowledge in the art teaches how to achieve such a pharmacological activity. "Testing for full safety and effectiveness...is more properly left to the Food and Drug Administration (FDA). Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings." *In re Brana*, 34 USPQ2d 1436, 1442 (Fed. Cir. 1995). Here, the specification provides abundant evidence that compositions of Aβ and adjuvant have pharmacological activity. Further, such activity has been confirmed in a clinical trial as described in the attached declaration by Dr. Martin Koller. In these circumstances, it is submitted that speculation that the compositions may not cure every aspect of Alzheimer's disease or may not be entirely free from side effects is not detrimental to enablement.

¶17. The Examiner alleges the specification does not provide guidance or examples that would enable a skilled artisan to use the pharmaceutical composition comprising PrP in a patient. The Examiner also alleges that predicting the efficacy of the compositions in treating a prion-based disease from a different unrelated immunogenic preparation is unpredictable.

Initially, it is submitted that enablement of a pharmaceutical composition does not require teaching how to use the composition in a patient. A pharmacological activity is itself "obviously beneficial to the public." For the reasons discussed above, it is sufficient that the specification, in combination with knowledge in the art, teach how to obtain a pharmacological activity from the composition.

Second, the specification provides considerable guidance regarding pharmaceutical compositions comprising PrP or other amyloid component and an adjuvant. The specification discloses a general strategy and principles whereby administration of such a

composition generate antibodies to the amyloid component, and the antibodies remove and/or prevent further accumulation of pathological deposits of the amyloid component. The strategy of making such compositions and administering them to a subject so as to generate antibodies are closely analogous irrespective of which amyloid component is incorporated into the composition.

With respect to the Examiner's position that administration of Aβ42 is not predictive of other amyloid peptide based diseases, applicant notes evidence showing analogous results for two other amyloid peptides, namely, synuclein and PrP. The specification describes an example in which antibodies to various epitopes of Aβ and antibodies to synuclein were tested in an *ex vivo* assay for capacity to clear amyloid deposits from brain tissue in the presence of phagocytic cells (*see* pp. 113-117). The antibodies to Aβ were also tested in the PDAPP mouse model. The results from the *ex vivo* model show excellent correlation with those *in vivo*: antibody to Aβ that cleared deposits *ex vivo* also cleared deposits *in vivo*. Because antibodies to synuclein were found to clear amyloid deposits characteristic of Alzheimer's disease *ex vivo* and because of the excellent correlation between *ex vivo* and *in vivo* results, one would reasonable expect that antibodies to synuclein would also clear amyloid deposits *in vivo*. Thus, administration of synuclein with an adjuvant is reasonable expected to clear amyloid deposits in similar fashion to Aβ. Likewise, closely analogous results have been reported for administration of PrP or antibodies thereto as discussed in the Sigurdsson *et al.* papers cited above.

Although the precursor proteins in different amyloid diseases do not share sequence homology or related native structure, the morphology and properties of all amyloid fibrils are remarkably similar (Sunde *et al., J. Mol. Biol.,* 273[3]:729-739 [1997], a copy of which is attached hereto). All give similar high-resolution X-ray fiber diffraction patterns, consistent with a helical array of beta-sheets parallel to the fiber long axis, with the strands perpendicular to this axis irrespective of the nature of their precursor proteins *(Id)*. Given the common structure of amyloid deposits in different diseases, the likelihood that immunization of any amyloid peptide with an adjuvant in an appropriate regime will generate antibodies, and the demonstration that antibodies to three different amyloid peptides (Aβ, synuclein and PrP) have clearing activity against amyloid deposits, it is likely that what has been observed for Aβ in

treatment of Alzheimer's disease is generally true for other amyloid peptides in treatment of other amyloidogenic diseases.

¶18. No comments are needed.

¶19. The Examiner notes that there are a number of distinct prion-based diseases that share the common element of a prion protein but are caused by different mutations or isoforms. The Examiner takes the view that undue experimentation would be required on how each individual isoform and mutation will affect the immune system of the patient.

As discussed above, the application discloses a general strategy in which pharmaceutical compositions comprising an agent and adjuvant generate an antibody response against an amyloid component and thus remove the amyloid component or reduce its further accumulation in amyloid deposits in a subject. This strategy accommodates different amyloidogenic diseases characterized by different amyloid components by appropriate selection of the agent in the composition. For example, to treat Alzheimer's disease, one can select an agent that generates an antibody response to Aβ, and to treat prion-based disease, one can select an agent that generates an antibody response to the prion component of the disease. Insofar as different prion-based diseases are characterized by different mutations or isoforms of prion protein, the different subtypes of disease can similarly be accommodated, if necessary, by selection of an agent that induces antibodies to the prion form present in the appropriate subtype. Mutagenic or isoform variation between different forms of prion-based disease does not, however, necessarily imply that a different agent is needed for treatment of each disease subtype. Although a particular mutation in a prion may be critically affect the path of disease, it is less likely to change substantially the immunoreactivity of the fragment. Thus, many antibodies against one form of prion protein are likely to react with other form notwithstanding mutagenic or isoform variation. For example, the antibodies shown to have pharmacological activity against prion-based disease by Sigurdsson *et al.*, *Neuroscience Letters,* 336, 185-187 (2003) were all raised against normal PrP rather than the pathogenic form, ASc. For these reasons, it is

submitted that general strategy for design of pharmaceutical compositions can accommodate variations between prion protein in different types of prion-based disease.

¶20. The Examiner cites Wisniewski as teaching that use of a nontoxic form of amyloid protein is crucial for the success of any immune based therapies. Tal is cited as teaching that immunization with Freund's Adjuvant alone has the same immunogenic effect as Freund's adjuvant with PrP.

As in treatment of any disease, it can be acknowledged that the ideal therapeutic is one that is entirely free of toxicity. However, this ideal is rarely, if ever, realized and is certainly well beyond the requirements of enablement. As was discussed above, a pharmacological composition is enablement if the specification teaches how to obtain a pharmacological activity using the composition. The results of Tal appear anomalous, and contrary to those of Sigurdsson *et al.*, *Am. J. Pathol.* 161, 13 (2002) in which immunization with prion protein and CFA significantly delayed onset of disease relative to immunization CFA alone. It is premature to draw any firm conclusions from Tal's results unless these results can be confirmed or further explained by subsequent work. In any event, Tal's results tend to support rather than contradict the position that a composition of a prion protein and adjuvant has ct pharmacological activity in treating prion based disease.

¶21. The Examiner cites Smits and Schreunder and Aguzz and Weissman for the view that administration of prion protein may cause a prion disorder rather than alleviate it. However, the prion proteins in the references were not administered with an adjuvant or otherwise under conditions calculated to generate antibodies. The use of an adjuvant, as recited in the presently claimed composition, favors the desired beneficial response. Applicant also reiterates the comments above that the possibility of side effects does not negate enablement for a pharmaceutical composition.

¶¶22-24. The Examiner cites Diomede as discussing possible toxicities of prion protein to certain types of cells *in vitro*. Sigurdsson is cited as discussing forming an Aβ variant

to reduce toxic side effects. Applicant reiterates that enablement of a pharmaceutical composition requires a teaching of pharmacological activity, not one of freedom from all side effects.

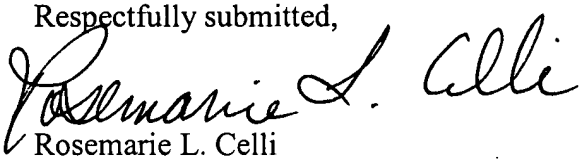
¶25. Claims 1-6 and 9-10 stand rejected as anticipated by Prusiner. Prusiner is cited as teaching a pharmaceutical composition comprising PrP^{Sc} with complete Freund's adjuvant. It is respectfully submitted that the rejection is moot in view of the amendment of the claims to recite an adjuvant that is pharmaceutically acceptable for use in humans. Complete Freund's adjuvant promotes a strong and prolonged immune response and is typically used in the generation of antibodies to a given antigen in laboratory animals. However, a frequent side effect of administering Freund's adjuvant is the induction of aggressive and persistent granulomas (*see* Harlow & Lane, *Antibodies: A Laboratory Manual*, CSHL [1988] at p. 98). For this reason, Freund's adjuvant is never used in humans. Accordingly, Freund's adjuvant is not an adjuvant that is pharmaceutically acceptable for human administration, as specified in the amended claims.

Moreover, although adjuvants suitable for human administration were certainly well known, one would have no motivation to use one unless therapeutic administration were contemplated. The teaching that administration of pharmaceutical composition comprising an agent effective to induce an immune response against an amyloid component in a patient and an adjuvant comes from the present application and not the prior art.

¶26. Claims 16 and 9-10 stand rejected as anticipated by Prusiner, US 5,846,533. This rejection raises the same issue as 25 and applicant responds in the same way.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



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